Consequences of Presentation With Advanced HIV Disease in Pregnancy: Data From a National Study in Italy

Marco Floridia, MD, Enrica Tamburrini, MD,† Giulia Masuelli, MD,‡ Giovanni Guaraldi, MD,§ Atim Molinari, MD,‖ Irene Cetin, MD,¶ Serena Dalzero, MD,# Arsenio Spinillo, MD,** Giuseppina Liuzzi, MD,†† Carmela Pinnetti, MD,†† Ilaria Vicini, MD,‡‡ Paula Castelli, MD,§§ Valentina Sacchi, MD,# and Marina Ravizza, MD,# on behalf of the Italian Group on Surveillance on Antiretroviral Treatment in Pregnancy*

Abstract: Among 469 women with a diagnosis of HIV in pregnancy, 74 (15.8%) presented with less than 200 CD4 cells per cubic millimeter. The only variable significantly associated with this occurrence was African origin (odds ratio: 2.22, 95% confidence intervals: 1.32 to 3.75, $P = 0.003$). Four women with low CD4 (5.6%), compared with none with higher CD4 counts, had severe AIDS-defining conditions ($P < 0.001$) during pregnancy or soon after delivery, and one transmitted HIV to the newborn. Early preterm delivery (<32 weeks) was significantly more frequent with low CD4 (6.2% vs. 1.4%, $P = 0.015$). An earlier access to HIV testing, particularly among immigrants of African origin, can prevent severe HIV-related morbidity.

Key Words: HIV, pregnancy, advanced HIV disease, HIV vertical transmission, African provenance

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From the *Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Rome, Italy; †Department of Infectious Diseases, Catholic University, Rome, Italy; ‡Department of Obstetrics and Neonatology, Città della Salute e della Scienza Hospital, and Universiy of Turin, Turin, Italy; §Department of Medical Specialties, Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy; ‖Department of Infectious Diseases and Hepatology, Azienda Ospedaliera di Parma, Parma, Italy; ¶Department of Obstetrics and Gynaecology, Luigi Sacco Hospital and University of Milan, Milan, Italy; #Department of Obstetrics and Gynaecology, DMSD San Paolo Hospital Medical School, University of Milan, Milan, Italy; **Department of Obstetrics and Gynaecology, University of Pavia, IRCCS Policlinico San Matteo, Pavia, Italy; ††INMI Lazzaro Spallanzani, Rome, Italy; ‡‡Department of Obstetrics and Gynaecology, City Hospital, Prato, Italy; and §§Operative Unit of Infectious Disease, Hospital of Macerata, Macerata, Italy.

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Ethics approval was obtained on September 28, 2001, from the Ethics Committee of the INMI Lazzaro Spallanzani in Rome (ref. deliberation no. 578).

Correspondence to: Marco Floridia, MD, Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy (e-mail: marco.floridia@iss.it).

INTRODUCTION

Despite the significant improvements achieved in the treatment and prognosis of HIV infection and the widespread efforts aimed at increasing HIV testing among sexually active individuals, late diagnosis of HIV is still frequent in several Western countries, with significant clinical and therapeutic challenges, additional costs, and increased morbidity and mortality.[1–3] Several studies have evaluated the prevalence and correlates of a late diagnosis in the course of HIV infection, showing a variety of potential predictors, that include male gender, younger age, foreign nationality or migrant status, history of drug use, transmission through heterosexual contacts, lower level of education, and poorer clinical status.[4–8]

This issue, however, has rarely been addressed in pregnant women,[9,10] although they represent a particularly vulnerable population, characterized by specific clinical and therapeutic requirements and by an additional risk of pregnancy-related complications.[11] Given the clinical relevance of this issue, we used data from a national study of pregnant women with HIV to analyze the proportion of newly diagnosed pregnant women with advanced disease, the determinants of this occurrence, and its impact on maternal and neonatal outcomes.

METHODS

Data from the National Program on Surveillance on Antiretroviral Treatment in Pregnancy were used.[12] This is a national observational study of pregnant women with HIV established in Italy in 2001, reflecting current clinical care. Only HIV-positive pregnant women are included, and no specific guidance is given in terms of treatment of HIV infection or prophylaxis for mother-to-child transmission, which is decided by the treating physician. Laboratory and clinical data are collected from hospital records of Obstetrics, Infectious Diseases, and Pediatrics departments, following the women's consent. Information and measurements are collected at routine visits performed during pregnancy (with no restrictions in gestational age at entry into prenatal care), at delivery, during postpartum, and during a follow-up of mothers and newborns for up to 18 months. For the present analysis, we considered all pregnancies with known dates of

HIV diagnosis and of last menstrual period and compared baseline characteristics and clinical outcomes according to the presence of advanced HIV disease. Time of diagnosis was categorized as "in pregnancy" or "before pregnancy" using the date of last menstrual period as threshold, and advanced disease was defined by a CD4 cell count below 200/mm^3 or the presence of an AIDS-defining clinical condition. Major birth defects were defined according to the Antiretroviral Pregnancy Registry criteria,[13] and gender- and gestational age–adjusted Z scores for birth weight were calculated according to national reference standards.[14] Preterm and early preterm delivery were defined as delivery before 37 and 32 completed weeks of gestation, respectively, and low and very low birth weight by values below 2500 and 1500 g, respectively. Cesarean section was considered elective if performed before the rupture of membranes and the onset of labor and nonelective if performed after the rupture of membranes, onset of labor, or both. Quantitative data were compared by Mann–Whitney U test, and the temporal trends were analyzed using the χ^2 test for trend. Contingency tables and the χ^2 test were used to compare qualitative variables and to estimate odds ratios and 95% confidence intervals for the relevant outcomes. P values below 0.05 were considered significant. All analyses were performed using the SPSS software, version 22.0 (IBM, Somers, NY).

RESULTS

As of October 8, 2014, the study database contained 2478 pregnancies with known date of HIV diagnosis. Rate of HIV diagnosis in pregnancy across the entire study period (2001–2014) was 23.8%, with no significant time trend observed ($P = 0.585$, χ^2 for trend). Among the 591 cases with HIV diagnosis in pregnancy, 469 (79.3%) had available information on CD4 count and/or HIV disease stage and were further analyzed. The rate of advanced disease among new HIV diagnoses in pregnancy was 15.8% (74/469), with no major temporal changes during the observation period (2001–2014: $P = 0.581$, χ^2 for trend). In 4 cases with CD4 cell count below 200/mm^3 (5.6%), an AIDS-defining clinical condition was diagnosed either in pregnancy or soon after delivery. These conditions were represented by 2 cases of neurotoxoplasmosis, one case of large B-cell non-Hodgkin lymphoma and one case who, at the same time, had esophageal candidiasis and *Pneumocystis* pneumonia. No cases of AIDS-defining events were observed among women diagnosed with HIV in pregnancy with more than 200 CD4 cells per cubic millimeter ($P < 0.001$).

Among women with a diagnosis of HIV in pregnancy, the only variable significantly associated with advanced disease was African origin (odds ratio: 2.22, 95% confidence intervals: 1.32 to 3.75, $P = 0.003$), whereas there was no significant association with age ($P = 0.395$), parity ($P = 0.642$), route of transmission ($P = 0.148$), and history of sexually transmitted diseases ($P = 0.469$).

The main maternal and neonatal outcomes are reported in Table 1. The 2 groups of newly diagnosed pregnant women with and without low CD4 had similar rates of undetectable HIV RNA at third trimester, mode of delivery, preterm delivery, and pregnancy complications. The infants from the 2 groups of mothers did not differ in birth weight (2950 vs. 2825 g, $P = 0.971$), Z score for birth weight (−0.22 vs. −0.20, $P = 0.989$), and in rates of low birth weight, major birth defects, and HIV transmission (Table 1). In addition to the above-reported significantly higher risk of being diagnosed with severe AIDS-defining clinical conditions, women with advanced disease also had a significantly higher rate of early preterm delivery (<32 weeks: 6.2% vs. 1.4%, $P = 0.015$), with a trend for more frequent occurrence of very low birth weight (<1500 g: 6.8% vs. 2.1%, $P = 0.093$).

DISCUSSION

This study explored late presentation with advanced disease in pregnant women with HIV, providing new information on a previously poorly studied population: a recent review from Siedner referring to adults diagnosed with HIV in sub-Saharan countries found few studies in pregnant women and provided no information on maternal and infant outcomes.[9] A more population-specific, although less recent, study conducted in Brazil between 2007 and 2009 found that the prevalence of late presentation (defined by less than 350 CD4 cells per cubic millimeter) was less than half in pregnant women (21.1%) compared with both nonpregnant women (56.0%) and men (55.4%).[10] The prevalence that we observed among pregnant women (15.8%), considering the lower CD4 threshold adopted (<200/mm^3), can be considered as consistent with the above findings. The data collected also indirectly confirm, compared with available national data, that in women diagnosed with HIV in pregnancy, presentation with low CD4 is less frequent compared with the general population: in the national study by Camoni et al[5], advanced disease at diagnosis involved 37.8% of all new HIV diagnoses reported in Italy during 2010–2011.

Despite the lower prevalence, the clinical impact of this condition was relevant because 4 women in this subgroup were diagnosed during pregnancy or soon after delivery with severe AIDS-defining conditions that required specific treatment. One of such cases was also associated with mother-to-child transmission of HIV. Importantly, among women diagnosed with HIV in pregnancy, only those with less than 200 CD4 cells per cubic millimeter seemed to be at risk of developing AIDS-defining conditions in pregnancy. Women with presentation in advanced disease had also a higher rate of early preterm delivery (<32 weeks), a condition which is known to be associated with significant infant morbidity because of prematurity-related complications.

The only variable significantly associated with presentation in advanced HIV disease was African provenance. This is consistent with other studies on late diagnosis in the general population.[1,2,15] Other studies have shown that pregnant women of African ethnicity are also significantly more likely to book late for antenatal care,[16] a condition that increases the risk of adverse maternal and infant outcomes, including HIV transmission.[17] Taken together, these observations strongly underline the need to promote an earlier

TABLE 1. Main Maternal and Infant Outcomes According to the Presence of Advanced Disease at Presentation

	All (%)	<200 CD4%	≥200 CD4%	Odds Ratio	95% Confidence Intervals	*P*
AIDS-defining conditions during pregnancy or postpartum (n: 442)	*0.9*	*5.6*	*0*	*NC*	*NC*	*<0.001*
On antiretroviral treatment at delivery (n: 453)	97.8	98.6	97.6	1.689	0.211 to 13.543	0.622
HIV RNA < 50 copies at third trimester (n: 371)	51.8	45.9	52.9	0.755	0.435 to 1.310	0.318
Preterm delivery (<37 wk, n: 420)	16.0	16.9	15.8	1.088	0.536 to 2.209	0.816
Early preterm delivery (<32 wk, n: 420)	*2.1*	*6.2*	*1.4*	*4.590*	*1.199 to 17.576*	*0.015*
Vaginal delivery (n: 422)	2.4	0	2.8	NC	NC	0.168
Nonelective cesarean delivery (n: 421)	14.3	13.6	14.4	0.941	0.439 to 2.019	0.876
Delivery complications (n: 418)	7.4	7.8	7.3	1.069	0.395 to 2.896	0.895
Low birth weight (<2500 g, n: 384, twins included)	19.0	16.9	19.4	0.849	0.408 to 1.768	0.661
Very low birth weight (<1500 g, n: 384, twins included)	3.1	6.8	2.1	2.882	0.839 to 9.898	0.093
Apgar score <7 (n: 338, twins included)	0.9	1.8	0.7	2.491	0.222 to 27.946	0.459
Birth weight Z score < 10th percentile (n: 364, singletons only)	9.3	5.4	10.1	0.506	0.149 to 1.715	0.274
Birth weight Z score > 90th percentile (n: 364, singletons only)	8.0	7.1	8.1	0.871	0.291 to 2.606	0.805
Major birth defects (n: 408)	2.2	0	2.6	NC	NC	0.194
HIV transmission (n: 274)	0.7	2.3	0.4	5.476	0.336 to 89.27	0.181

Values for the outcomes significantly associated with advanced disaese are reported in italic. NC, odds ratio and confidence intervals not calculated.

access to HIV testing and care among immigrants, particularly of African origin, removing any potential restriction that may delay access to health care.

In term of strengths and weaknesses, the determinants and consequences of a presentation to antenatal care with undiagnosed advanced HIV disease in a national cohort of pregnant women have been described for the first time. The new information provided can be relevant for prevention strategies targeted to populations at risk and for calculating the costs of the maternal and neonatal morbidity (AIDS events and HIV transmission) associated with late presentation.

The main limitation of this study is the relatively small number of women with advanced disease, which may have precluded the possibility to detect other relevant associations. This is, however, not the consequence of a limited sample size but rather of the fact that presentation with advanced disease, although associated with clinically significant disease, is fortunately relatively rare among pregnant women compared with the general population. It is important to note that the number of women presenting with advanced disease was adequate to detect significant outcome differences with women with less advanced CD4 deterioration. As for other observational cohorts, we also cannot rule out some inherent sources of bias, such as missing data, participation of selected centers, or selective case reporting.

In conclusion, this study identified African origin as a determinant of presentation in advanced disease and showed that this occurrence is associated with clinically important adverse outcomes; efforts and interventions are still needed to promote an earlier access to HIV testing that can be significantly effective in preventing maternal clinical progression and infection of the newborn with HIV.

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APPENDIX. The Italian Group on Surveillance of Antiretroviral Treatment in Pregnancy

Project coordinators: M. Floridia, M. Ravizza, E. Tamburrini.

Participants: M. Ravizza, E. Tamburrini, F. Mori, P. Ortolani, E. R. dalle Nogare, F. Di Lorenzo, G. Sterrantino, M. Meli, S. Polemi, J. Nocentini, M. Baldini, G. Montorzi, M. Mazzetti, P. Rogasi, B. Borchi, F. Vichi, B. Del Pin, E. Pinter, E. Anzalone, R. Marocco, C. Mastroianni, V. S. Mercurio, A. Carocci, E. Grilli, A. Maccabruni, M. Zaramella, B. Mariani, G. Natalini Raponi, G. Guaraldi, G. Nardini, C. Stentarelli, B. Beghetto, A. M. Degli Antoni, A. Molinari, M. P. Crisalli, A. Donisi, M. Piepoli, V. Cerri, G. Zuccotti, V. Giacomet, V. Fabiano, S. Coletto, F. Di Nello, G. Placido, A. Vivarelli, P. Castelli, F. Savalli, V. Portelli, F. Sabbatini, D. Francisci, L. Bernini, P. Grossi, L. Rizzi, S. Alberico, G. Maso, M. Airoud, G. Soppelsa, A. Meloni, M. Dedoni, C. Cuboni, F. Ortu, P. Piano, A. Citernesi, I. Bordoni Vicini, K. Luzi, A. Spinillo, M. Roccio, A. Vimercati, A. Miccolis, A. De Gennaro, B. Guerra, F. Cervi, C. Puccetti, E. Margarito, M. Contoli, M. G. Capretti, C. Marsico, G. Faldella, M. Sansone, P. Martinelli, A. Agangi, G. M. Maruotti, C. Tibaldi, L. Trentini, T. Todros, G. Masuelli, V. Frisina, I. Cetin, T. Brambilla, V. Savasi, C. Personeni, C. Giaquinto, M. Fiscon, R. Rinaldi, E. Rubino, A. Bucceri, R. Matrone, G. Scaravelli, C. Fundarò, O. Genovese, C. Cafforio, C. Pinnetti, G. Liuzzi, V. Tozzi, P. Massetti, A. M. Casadei, A. F. Cavaliere, V. Finelli, M. Cellini, G. Castelli Gattinara, A. M. Marconi, S. Dalzero, V. Sacchi, A. De Pirro, C. Polizzi, A. Mattei, M. F. Pirillo, R. Amici, C. M. Galluzzo, S. Donnini, S. Baroncelli, M. Floridia.

Pharmacokinetics: P. Villani, M. Cusato.

Advisory Board: A. Cerioli, M. De Martino, P. Mastroiacovo, M. Moroni, F. Parazzini, E. Tamburrini, S. Vella.

SIGO-HIV Group National Coordinators: P. Martinelli, M. Ravizza.